ANNALS OF SURGERY
Vol. 221, No. 1, 59–66

Long-Term Survival After Resection for Ductal Adenocarcinoma of the Pancreas

Is It Really Improving?

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Objective
The authors review their recent experience with resected pancreatic ductal adenocarcinoma.

Summary Background Data
Ductal adenocarcinoma of the pancreas has traditionally had a 5-year survival rate less than 10% after curative resection. Recently, several groups have reported markedly improved 5-year survival rates (approaching 25%) for patients undergoing curative resection.

Methods
Institutional experience with 186 consecutive patients (1981–1991) with pathologic diagnoses of ductal adenocarcinoma undergoing pancreatic resection was reviewed. Histologic specimens of all 3-year survivors (n = 31) were re-reviewed by two pathologists, one internal and one external; nonductal pancreatic cancers then were excluded.

Results
After histologic re-review, 12 patients did not have ductal adenocarcinoma, leaving a total of 174 patients for analysis (102 men, 72 women; mean age 63 years, range 34–82 years). Mean follow-up was 22 months (range 4–109). Classical pancreaticoduodenectomy was performed in 71%, pylorus-preserving resection in 9%, and total pancreatectomy in 20%. Hospital mortality was 3%. Twenty-eight patients (16%) had macroscopically incomplete resections; 98 (56%) had lymph node metastases within the resected specimens, and 21 patients (12%) had extensive perineural invasion. Overall actuarial 5-year survival was 6.8%. Five-year survival was greater for node-negative *versus* node-positive patients (14% *vs.* 1%, $p < 0.001$), and for smaller (<2 cm) *versus* larger tumors (20% *vs.* 1%, $p < 0.001$). The 5-year survival for the subset of patients with negative nodes and no perineural or duodenal invasion (69 patients) was 23% ($p < 0.001$). Mean survival of the 12 excluded patients was 53 ± 7 months compared with 17.5 ± 1 months in the 174 patients with ductal pancreatic cancer.

Conclusions
Five-year survival for patients undergoing pancreatic resection for lesions deemed to be clinically "curable" intraoperatively and histologically reviewed/confirmed to be ductal adenocarcinoma of the pancreas is approximately 7%. Survival is greater (23%) in the subset of patients with negative

nodes and no duodenal or perineural invasions. Pathologic review of all patients with pancreatic ductal cancer adenocarcinoma is mandatory if survival data are to be meaningful.

Ductal pancreatic adenocarcinoma, a lethal disease with an increasing incidence worldwide, carries a mortality close to 100%.[1-3] Operative resection provides the only chance for cure or long-term survival, provided that the tumor is localized and resectable at diagnosis. Since Whipple et al.[4] introduced pancreaticoduodenectomy for the treatment of ampullary tumors, the indications for this procedure were broadened to include ductal pancreatic cancers. The classic operation has gone through numerous modifications in attempts to specifically tailor it for better results with the treatment of ductal pancreatic cancer, either by preserving the pylorus,[5-8] by performing a total pancreatectomy,[9-11] or by extending resection margins to include a lymphadenectomy[12] or an en bloc resection of peripancreatic tissues.[13] In the past, the operative mortality associated with pancreaticoduodenectomy was as great as 30%[14,15] and evoked controversy and a call to abandon this procedure from surgical nihilists.[16,17] Even currently, the associated mortality remains high in centers without significant experience with this procedure.[18] In contrast, in centers with considerable experience in pancreatic surgery, the operative mortality of pancreaticoduodenectomy has declined to below 5%.[19-24] With this improvement in operative mortality, several selected centers have reported concomitant improvements in overall 5-year survivals to as great as 25%,[20,23,24] distinctly greater than multiple previous reports of <10%.[11,13,14,21,25-33] Because of these reports, we wondered whether the results with attempted curative resection truly were improving. Thus, we reviewed our recent experience (1981–1991) with resection of biopsy-proven ductal adenocarcinoma of the pancreas.

METHODS

We retrospectively reviewed the medical records of all patients undergoing potentially curative resections listed as having histologically proven pancreatic ductal adenocarcinoma between the years 1981 and 1991. We excluded patients with cancers arising in either the bile duct, duodenum, or ampulla of Vater, and endocrine tumors of the pancreas, pure intraductal tumors of the pancreas, and those patients who had undergone pancreatectomies primarily for palliation. Multiple demographic, clinical, and laboratory parameters were abstracted with special emphasis on histologic diagnosis, operative procedures, and survival. Histologic specimens were re-reviewed by two independent pathologists, one internal (T.V.C.) and one external (see acknowledgement); all re-reviewed nonductal pancreatic cancers then were excluded.

Follow-up averaged 22 months (range = 4–109 months) and was 100% complete either through the Mayo Tumor Registry or by direct patient contact. Survival curves were constructed using a Kaplan-Meier analysis, and prognostic variables were determined using a Cox proportional regression analysis and a log-rank test. Significant differences were accepted at the 5% level. Data will be presented as mean values (±SEM).

RESULTS

Patient Population

Between 1981 and 1991, we attempted clinically "curative" pancreatic resections in 186 patients with histologically classified ductal pancreatic cancer. However, on re-review of all 3-year survivors, 12 patients were excluded because of a change in diagnosis to islet cell tumor (3 patients), ampullary carcinoma (4 patients), cystadenocarcinoma (3 patients), cholangiocarcinoma (1 patient), and intraductal mucinous hypersecretory tumor (1 patient). This left 174 patients with confirmed ductal pancreatic adenocarcinoma, which comprises the study group for the remainder of this report. Their mean age (±SEM) was 63 ± 1 years (range = 34–82 years), with 102 men and 72 women, giving a male predominance of 1.4:1. Forty-six patients (31%) were older than 70 years of age. There was no significant difference between the ages of the genders.

Preoperative Evaluation

When stratified according to their preoperative risk factors (Table 1), 105 patients (60%) had at least one major risk factor. Most risk factors involved the cardiovascular system, including active coronary artery disease in 45 patients, 21 of whom had suffered myocardial infarctions and 1 of whom had undergone a heart transplantation.

Preoperative laboratory results demonstrated a mean serum bilirubin level of 8.8 mg/dL and an albumin level of 3.7 g/dL; 39 patients (22%) had a bilirubin level of >15 mg/dL, and 43 patients (25%) had a serum albumin level of <3.0 g/L.

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Accepted for publication May 23, 1994.

Table 1. RESECTED PANCREATIC ADENOCARCINOMA: PREOPERATIVE RISK FACTORS (174 PATIENTS)

	Patients	Percent
Cardiovascular system		
Active coronary artery disease	45	26
Valvular disease	6	3
Hypertension	39	22
H/O myocardial infarction	21	12
H/O stroke	5	3
H/O heart transplantation	1	~1
Respiratory system		
Chronic obstructive pulmonary disease	26	15
Smoking	37	21
General		
Chronic renal failure (on dialysis)	4	8
Diabetes mellitus	26	15
Alcoholism	7	4
Morbid obesity	12	7
Prior abdominal surgery		
Biliary bypass	46	26
Abdominal malignancy	8	4
Miscellaneous*	95	54

* Includes peripheral arterial occlusive disease, hepatic cirrhosis, hyper- and hypothyroidism, H/O pulmonary infarction/emboli, multiple deep vein thromboses, non-abdominal malignancies.

Forty-six patients initially had been diagnosed and treated elsewhere and had undergone biliary bypasses; eight other patients had undergone previous resections of unrelated intra-abdominal malignancies (i.e., colon, uterus, and ovary).

Operative Procedures

Pancreatic resection was performed by 16 different surgeons, although 76% of the resections were performed by 4 surgeons. Classic Whipple resections (pancreatoduodenectomies) were performed on 123 patients (71%), followed by total pancreatectomies on 20%, and pylorus-preserving pancreaticoduodenectomies on the remaining 9%. No patient had a regional pancreatectomy, as described by Fortner,[13] and no one had an extended lymphadenectomy, as described by Ishikawa et al.[12] When comparing all patients undergoing exploration for potential resection, the overall resectability rate doubled during the study period from 12% during the years 1981 to 1985 to approximately 25% from 1985 to 1991. All 174 patients underwent pancreatic resections for lesions deemed to be resectable both preoperatively and at the intraoperative assessment by the surgeon, although the resections were macroscopically incomplete in 28 patients (16%). We have included these latter 28 patients in our analyses throughout this manuscript (even though they had histologically noncurative resections); their inclusion is justified because we believe it is more realistic to include such patients when discussing radical potentially curative resections for patients with pancreatic cancer.

Histopathologic Staging

Using Broders' grading system, 93 patients (53%) had grade 3 tumors, and 78 patients (45%) had grade 2 tumors; 3 patients (2%) only were found to have well-differentiated grade 1 ductal adenocarcinoma. Histologic review demonstrated tumor invasion into the duodenum in 36 patients (21%) and extensive perineural invasion in 21 patients (12%). In 98 patients (56%), metastatic involvement of lymph nodes within the resected specimen were noted primarily in the retropancreatic region, both inferiorly or superiorly to the head of the pancreas. Based on the largest dimension, the mean tumor size was 3.1 cm (range, 0.9–6.1 cm). There were 42 patients (24%) with tumors smaller than 2 cm, and 56 patients (32%) had tumors greater than 4 cm. Patients also were stratified according to stage using the TNM classification,[34] in which T1 tumors were smaller than 2 cm, T2 tumors were greater than 2.1 cm, and T3 stage indicated direct extension into the duodenum or bile duct. Similarly, NO represented no lymph node metastases, N1 indicated peripancreatic metastases, and N2 indicated regional lymph node metastases. The majority of patients (98; 57%) had stage III tumors (Table 2).

Mortality and Morbidity of Pancreatectomy

The in-hospital operative mortality was 3%. The five deaths occurred secondary to postoperative acute myo-

Table 2. RESECTED PANCREATIC ADENOCARCINOMA: STAGE AND GRADE (174 PATIENTS)

Stage*	Patients (%)
Stage I	64 (36)
T1N0M0	41
T2N0M0	23
Stage II	
T3N0M0	12 (7)
Stage III	98 (57)
T1N1M0	34
T2N1M0	30
T3N1M0	34

* Includes the 28 patients with histologically positive margins.

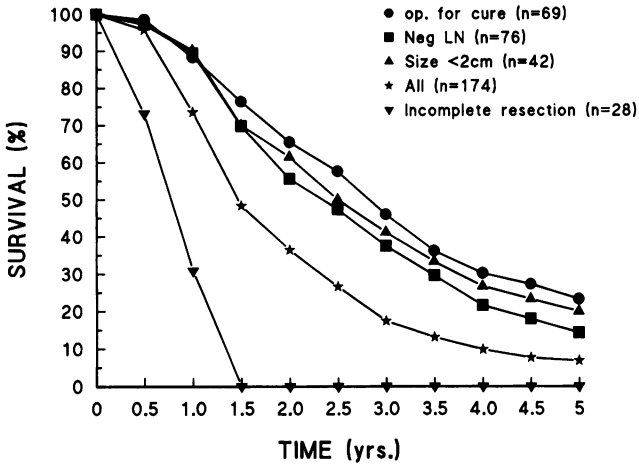

Figure 1. The actuarial 5-year survival according to various parameters.

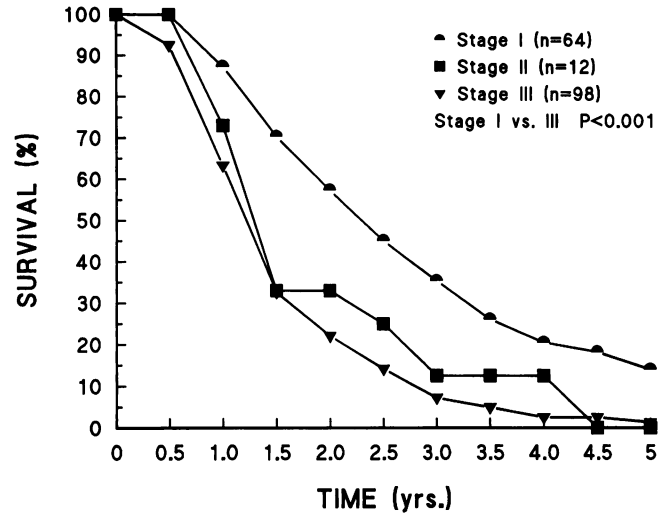

Figure 3. Actuarial survival according to pathologic stage.

cardial infarction, respiratory failure, pancreatic anastomotic leak and sepsis, biliary anastomotic leak and sepsis, and severe postoperative bleeding.

Morbidity remains significant.[35] One third of our patients (60 patients) had major postoperative complications, including anastomotic leakage (pancreatic, biliary, or gastric), hemorrhage, gastrointestinal fistulae, necrotizing pancreatitis, and intra-abdominal sepsis. Seventeen patients (10%) required re-operation for the aforementioned complications.

Survival

Overall 5-year actuarial survival for the 174 patients was 6.8%, with a median survival of 17.5 ± 1 months (Fig. 1). The 5-year survival in those 146 patients with a histologically curative resection was 12%. Recurrent pancreatic carcinoma was documented in 112 patients (64%) at a mean of 12.2 months (range = 2–37 months). The recurrence occurred locally in 38 patients at a mean of 13.1 months postoperatively, whereas distant metastases in the liver (42 patients), lung (11 patients), and diffuse peritoneal seeding (21 patients) occurred after mean intervals of 11, 13, and 15 months, respectively.

The absence of nodal metastases in the operative specimen conferred a definitive survival advantage (Fig. 2). Patients without lymph node metastases (n = 76) had greater 5-year survival than patients (n = 98) with at least one lymph node metastasis (14% *vs.* 1%, $p < 0.001$). Stage significantly affected survival with 5-year survival rates of 14%, 0%, and 1% for stages I (n = 64), II (n = 12) and III (n = 98), respectively ($p < 0.001$) (Fig. 3). When stratified according to the various subsets of these three stages (Fig. 4), there were no 5-year survivors in the sub-

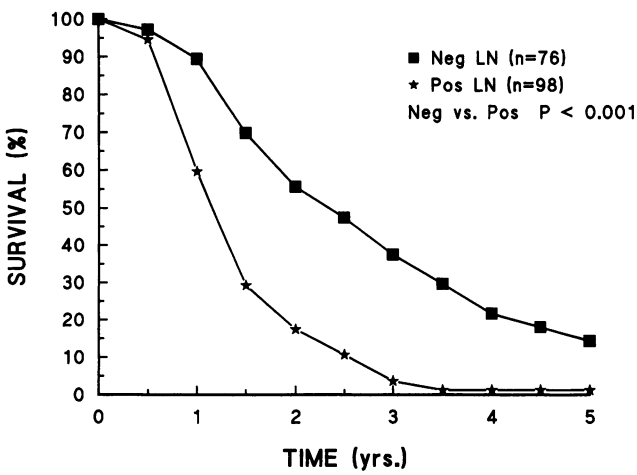

Figure 2. Actuarial 5-year survival rate according to lymph node involvement.

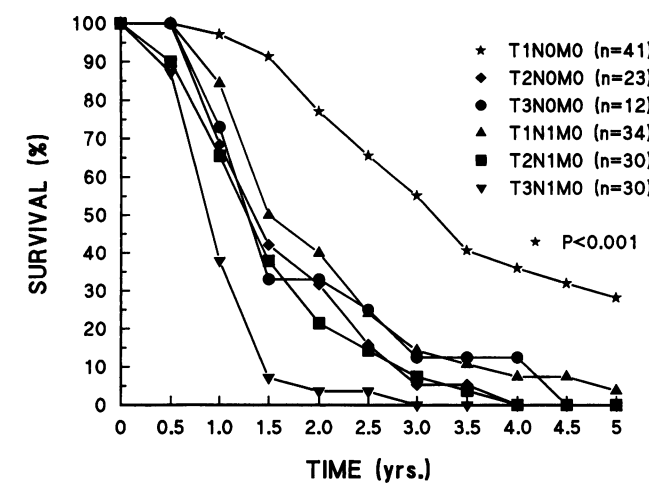

Figure 4. Actuarial survival in the various subsets of TNM staging.

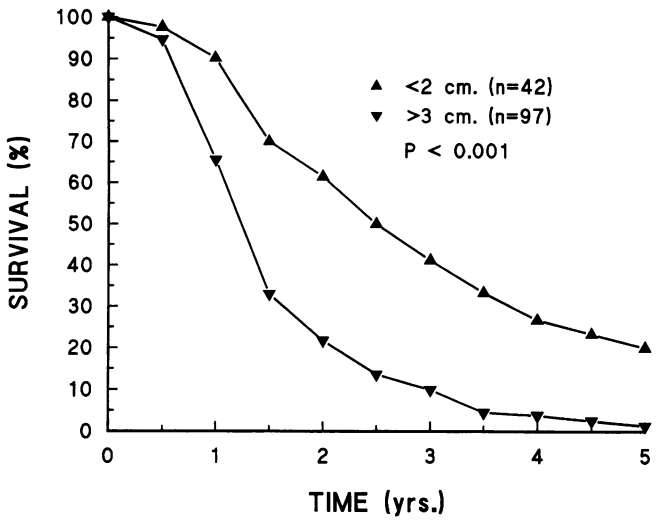

Figure 5. Actuarial 5-year survival according to tumor size.

groups of patients with T2NOMO, T3NOMO, and T2N1MO tumors; with T3N1MO disease (34 patients), there were no 3-year survivors. By contrast, the 5-year survival rates for patients with T1N1MO (34 patients) and T1NOMO (41 patients) disease were 4% and 23%, respectively (Fig. 4), showing again the negative influence of nodal metastases on survival. When stratified according to tumor size only, the 42 patients with a tumor ≤ 2 cm had a 20% 5-year survival rate compared with 1% ($p < 0.001$) for patients with tumors greater than 3 cm (Fig. 5).

As expected, the worst prognosis was observed for the 28 patients in whom macroscopically incomplete resections were done. None of these patients survived 18 months, with a mean survival of only 9 months. The most favorable subset was the 69 patients who had complete resections, negative lymph nodes, and neither extensive perineural invasion nor tumor infiltration into the duodenum; their 5-year survival rate was 23% (Fig. 1).

Other Factors Affecting Survival

The use of adjuvant forms of chemotherapy or radiation therapy had no apparent effect on survival (Fig. 6). Patient age, sex, preoperative bilirubin level, albumin level, and even Broders' tumor grading also had no significant ($p > 0.05$) effect on long-term survival. The 42 patients who had undergone previous operations had a 5% 5-year survival rate that was not different from that of the overall survival rate ($p > 0.05$).

We also tracked the 12 patients who were excluded from our study after pathologic re-review. Their overall disease staging was more favorable; 8 patients had stage I, two had stage II, and two had stage III disease, and their mean survival was 53 ± 7 months compared with 17.5 ± 1 months in the 174 patients with ductal adenocarcinoma of the pancreas.

Using a log-rank test, we identified the following favorable prognostic factors that increase long-term survival of patients when compared with the overall group of patients with ductal pancreatic cancer: negative lymph nodes ($p < 0.01$); tumor size ≤ 2 cm or stage I disease ($p < 0.001$); T1NOMO stage ($p < 0.0001$); and patients with the combination of negative nodes, lack of perineural invasion, and lack of duodenal infiltration ($p < 0.001$). In contrast, positive microscopic lymph nodes in the specimen ($p < 0.05$) and incomplete resection ($p < 0.001$) were bad prognostic factors.

DISCUSSION

Pancreatic ductal cancer usually has been considered a fatal disease. The majority of patients have unresectable disease at the time of diagnosis and die within a mean of 6 months. The small minority who prove to have clinically resectable neoplasms and undergo resections have a longer mean survival (18–24 months), but in most experience, less than 10% survive 5 years or longer. Recently, however, two separate groups have reported distinctly more optimistic results after curative resection for ductal adenocarcinoma of the pancreas in the most recent decade. Trede et al.[23] from Mannheim, Germany, have noted a 25% 5-year survival for all patients (n = 133) undergoing radical pancreaticoduodenectomies for ductal cancer. Similarly, Cameron's group from the Johns Hopkins Hospital[20] have reported a 5-year survival of 19% for a similar group of patients (n = 89). These optimistic results and those suggested by Warshaw's group[36] are so different from past reports that one

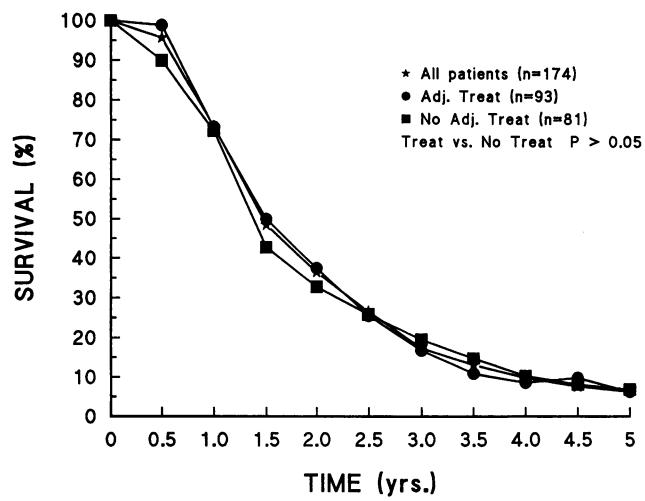

Figure 6. Actuarial 5-year survival according to use of postoperative adjuvant therapy.

might interpret these findings in one of several ways. Either the biology of adenocarcinoma of the pancreas has changed, patient selection and operative technique, combined with postoperative adjuvant therapy, has improved markedly, or these groups have included only those patients with pathologically curative resections, deleting those with macroscopically positive margins (16% in our series). These concepts stimulated us to critically review our most recent results with potentially curative resections of histologically confirmed ductal adenocarcinoma of the pancreas.

Our results at the Mayo Clinic differ markedly from these encouraging reports in several ways. First, we specifically re-reviewed (one internal and one external pathologist) the histopathology of all patients classified with ductal cancer who survived at least 3 years. Indeed, 12 of the 31 cases (more than one third) re-reviewed among the total 186 patients did not have ductal adenocarcinoma, but other tumors known to carry a more favorable prognosis. Second, we included all patients who underwent what the operating surgeon believed to be potentially curative resections at the time the decision was made to proceed with resection. Obviously, this approach will include patients with gross or microscopically involved margins along the uncinate process or the pancreatic remnant not noted on intraoperative frozen section histologic examination. Although we further analyzed subgroups to exclude these patients with noncurative resections, we believe our approach is more representative of everyone's experience and involves an objective report of what one should expect when deciding to perform a potentially curative pancreaticoduodenectomy for ductal cancer of the pancreas.

With this approach, we found that the 5-year survival for all patients undergoing pancreaticoduodenectomies for histologically confirmed ductal adenocarcinoma of the pancreas (n = 174) was 6.8%, not markedly improved over most past reports from our institution[10,11] and elsewhere.[25,27,32,33,36–38] When one excludes those patients who had noncurative resections with gross or microscopically involved margins (n = 28 patients or 16% of the total group), 5-year survival increased to 12%. This represents the expected survival in all patients who underwent classical pancreaticoduodenectomies. We did not perform an extended lymphadenectomy as advocated by Trede's group,[23] but neither did the Johns Hopkins group.[19,20,24] An added benefit of extended lymphadenectomy for ductal adenocarcinoma of the pancreas is not documented.

Although the overall 5-year survival remained a dismal 6.8%, there were selected subgroups with better prognoses. The absence of metastatically involved lymph nodes within the specimen increased survival to 14% (n = 76), yet this represented only 43% of the total group of patients undergoing resections. Similarly, the subgroup of patients with tumors $\leq$ 2 cm (n = 42, 24% of total) had a 20% 5-year survival; the majority of these patients (31 of 42) had no metastatic nodal disease. The most favorable group included patients with complete resections, negative nodes, and no extensive perineural or duodenal invasion (n = 69, 40% of the total group), who had a 5-year survival of 23%. These results are consistent with the findings of others.[36]

Our study also confirmed the prognostic significance of various gross and histologic parameters. Prognosis was decreased significantly with metastatic lymph nodes, an increasing clinicopathologic stage ($p \leq 0.01$ in each), but only marginally with perineural or duodenal invasion. We were unable to show a definite survival advantage for the use of postoperative adjuvant chemotherapy or radiation therapy, as suggested by the Kalser and the GITC groups[39,40]; however, these patients were treated off protocol—usually in their home community, were not randomized, and had multiple different regimens that we could not control.

The median and actuarial 5-year survival rates in our patients of 17.5 months and 6.8%, respectively, represent only minor and substantially small improvements over the last two decades. Although other reported median (or mean) survival periods range from 11 to 20 months, there is an enormous variation for the crude 5-year survival rates ranging from 0% to 25%[10,11,15,19–33,36–38] for all resected patients without a breakdown into subgroups.[27–30,38,41–44] Stratification of patients into subgroups according to various prognostic factors results in substantially improved 5-year survival rates. Lymph node involvement in the resected specimen is reported in 43% to 88% of patients, depending on the thoroughness of the search, and is well proven to be a poor prognostic factor.[12,19–21,27–29,36–38,41–49] Such nodal involvement may be indicative of lymph nodal metastases in regions normally not resected during a classical pancreaticoduodenectomy, such as the para-aortic region.[45,46,49] Thus, Fortner[13] introduced the concept of a regional radical pancreatectomy to allow an en bloc resection with an extended lymphadenectomy; however, his results have not been convincing. Surgeons in Japan practice an aggressive approach toward pancreatic cancer,[48–51] but again, there seem to be conflicting data as far as the survival advantages of such an aggressive approach because of a greater associated morbidity and mortality and also because a prolonged survival has not been demonstrated convincingly except in certain selected subsets of patients. This is similar in some respects to new concepts involved with current approaches toward breast cancer, and some may argue that the same conclusions can be drawn here, namely that supraradical surgery for

pancreatic ductal cancer is not necessarily associated with better survival rates.

Tumor size is another prognostic factor that affects both lymph node involvement and survival. The greater the size of the primary tumor, the greater the incidence of lymph node metastases and vascular encasement and, thus, the less the survival.[21,23,30,45,47,49] Warshaw et al.[38] referred to 3 cm as the cut-off size between curable and noncurable tumors, whereas tumors of 4 cm or greater size rarely are resectable.[37,45,46] As mean tumor size decreases, resectability rate increases. There is some suggestion that in recent years, either the diagnosis is made at an earlier stage of the disease or the selection of patients is stricter—at least as measured by tumor diameter. In a recent report from the Johns Hopkins group, mean tumor size had decreased to 3 cm, with 36% of the patients harboring tumors smaller than 2 cm.[20] This is believed to be important because 5-year survivors had a mean tumor size of 2.7 cm as opposed to 3.2 cm for nonsurvivors.[19,20] These data argue for attempts to make the diagnosis at an earlier stage of the disease. The mean tumor size in our patients was 3.1 cm, with only 24% of the patients having tumors smaller than 2 cm; 32% of our patients had tumors of 4 cm or greater.

As with other reports,[27,28,45,47,52] we have found that tumor staging is an important prognostic factor. Tumor grading, direct infiltration to local adjacent tissues, and perineural invasion are not considered prognostic factors[11,20,21,42,46,48] or at least not until 3 years after surgery.[50] Similarly, an incomplete resection forebodes an especially poor prognosis; none of the 28 patients in our series who underwent incomplete resections survived 18 months. Whether mean survival is improved by this type of palliative resection remains unknown.

Finally, of previously underestimated importance in dealing with long-term survival rates for a true ductal pancreatic adenocarcinoma is pathologic re-review. In our recent series, we excluded 12 patients (7%) to achieve a cohort group of true histologically reconfirmed invasive ductal pancreatic adenocarcinoma. The inclusion of those 12 patients, who had a mean survival of 54 months, would have markedly improved the 5-year survival rate. When Connolly et al.[29] reviewed their patients classified with ductal cancer of the pancreas, 17% of their patients did not have malignancies at all, and 29% were found not to have pancreatic ductal cancer. These findings argue strongly for the need to strictly re-review the histopathology of resected specimens by a nonbiased pathologist when reporting prolonged survival after resection of invasive ductal adenocarcinoma of the pancreas.

Although the overall results in managing patients with pancreatic ductal cancer remain discouraging, the only chance for cure is surgical resection. With improvements in preoperative selection and perioperative care, the operative mortality is less than 5% in centers with experience with pancreatic surgery. With 5-year survivals of approximately 20% in selected subgroups of patients with confirmed ductal adenocarcinoma of the pancreas, and with 5-year survivals of 30% to 60% in patients with periampullary neoplasms masquerading as ductal cancer but arising from the distal bile duct, the ampulla, the duodenum, or the islet tissue (islet cell cancers), a nihilistic nonoperative approach to patients with periampullary neoplasms presumed to be pancreatic adenocarcinoma is not justified. Whether new techniques of neoadjuvant chemo/radiation therapy,[39,40,44] extended lymphadenectomy,[45–51] regional pancreatectomy,[13,51] intraoperative radiotherapy,[52] or new approaches to postoperative adjuvant therapy will prove of benefit await controlled trials.

We reported one of the largest cohort series of patients with histologically confirmed ductal pancreatic adenocarcinoma. Although mortality rates after pancreatic resection have declined, long-term survival rates remain dismal. Favorable survival rates might therefore, be explained as the result of strict and better preoperative selection.

Acknowledgments

The authors thank Dr. David Klimstra from Memorial Sloan Kettering for his histopathologic review of tissue for us and Deborah I. Frank for her excellent secretarial support in the preparation of this manuscript.

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